

A Phase I Study of Subcutaneous “CYT 99 007” (Interleukin-7) in Patients with Refractory Non-Hematologic Malignancy

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1. STUDY OBJECTIVES

1.1. Primary objective

- Determine safety and, possibly, dose-limiting toxicity of biologically active doses of “CYT 99 007” (recombinant human IL-7) in the context of malignancy refractory to conventional therapies.

1.2. Secondary objectives

- Characterize biological effects of “CYT 99 007” as defined in the study end-points.
- Define the pharmacokinetic and pharmacodynamic characteristics of “CYT 99 007” (rhIL-7) in humans.
- Identify a range of biologically active doses of “CYT 99 007” (rhIL-7) in patients with refractory malignancy.
- Examine the anti-tumor effects of “CYT 99 007” in the context of a dose escalation strategy.

2. RATIONALE & BACKGROUND

IL-7 and Immune Development

The role of IL-7 in human immune development is indirectly confirmed in Severe Combined Immune Deficiency (SCID) patients who have markedly decreased numbers of T- and B-cells. At least three groups of patients with a SCID phenotype have mutations involving the IL-7 receptor or its signaling pathway. Only IL-7 deficiency is capable of reproducing in murine models most of the abnormalities of T cell development found in the SCID patients.

IL-7 and Cancer Therapy

- The potential benefits of recombinant human IL-7 in the treatment of cancer are centered on IL-7's immuno-modulatory effects, particularly those related to T cells.
- In murine models, IL-7 enhances anti-tumor immune responses both *in vitro* and in mice previously injected with tumor cells.
- IL-7 induces regression of established pulmonary metastases of Renca renal carcinoma.
- Mouse models of autologous transplant for metastatic breast cancer demonstrate that post-transplant administration of rhIL-7 not only improves T cell recovery, but also has additive therapeutic activity resulting in prolonged survival of the animals beyond what is achieved with chemotherapy and transplant alone.
- In human colon carcinoma xenograft mouse model, injection of rhIL-7 along with human lymphocytes results in a significant prolongation of survival.
- IL-7 induces tumoricidal activity of human peripheral monocytes.
- IL-7 activated killer cells can lyse allogeneic and autologous melanoma cells.
- IL-7 may also prove to be important in supporting immune reconstitution after bone marrow transplantation or intensive chemotherapy.

In summary, IL-7 may potentially have beneficial effects in patients with cancer by (1) supporting and augmenting anti-tumor T cell responses, (2) by augmenting T cell responses to anti-tumor immunizations (adjuvant in vaccination strategies), (3) by promoting T cell recovery following therapy-induced depletion .

3. ELIGIBILITY CRITERIA

3.1. Inclusion Criteria:

- Age \geq 18 years
- Diagnosis of malignancy (see exclusion criteria), histologically confirmed by the Laboratory of Pathology at each participating center (no central pathology review)
- Presence of incurable malignancy and failure of standard therapy for disease (either no response or 25% disease progression or new disease)
- Presence of measurable or evaluable disease
- Normal Ejection Fraction by MUGA or Echocardiogram
- DLCO/VA and FEV1 $>$ 50% of predicted on pulmonary function tests
- AST and ALT $<$ 3x the upper limit of normal
- Absolute Neutrophil Count $>$ 1000/mm³
- Platelets $>$ 100,000/mm³
- PT/PTT within 1.5x upper limit of normal
- Karnofsky performance status $>$ 70%
- Creatinine Clearance of $>$ 60 cc/min
- Stable CD3+ cell count $>$ 300 cells/mm³ in the peripheral blood—on four successive determinations over a period of no more than two weeks—immediately prior to study

entry ["stable" is defined as a coefficient of variation (standard deviation divided by the mean) of 20% or less; the fourth determination will decide the on-study date]

- Absence of corticosteroid therapy for more than 72 hrs in the two weeks prior to the start of the four peripheral CD3 count determinations
- Absence of cytotoxic therapy in the four weeks prior to the start of the four peripheral CD3 count determinations

3.2. Exclusion criteria

- Presence of potentially curable malignancy not yet treated with all appropriate standard therapies of known curative potential
- Determination during evaluation that a therapy incompatible with this study's eligibility criteria is in candidate's best interest, patient will be immediately withdrawn from consideration to receive appropriate treatment
- Hematopoietic malignancies
- Primary carcinoma of the lung
- Life expectancy of less than three months
- Documented HIV, hepatitis B, or hepatitis C infection.
 - A positive hepatitis B serology indicative of previous immunization (*i.e.*, HBs Ab positive and HBc Ab negative) is not an exclusion criterion
 - A positive hepatitis C serology is an exclusion criterion
- Concurrent cytotoxic or immunosuppressive therapies
- Medical need for chronic anticoagulation
- Resting blood pressure > 140/90
- Current need for palliative therapy as determined by principal investigator
- History of autoimmune disease
- History of severe asthma, presently on chronic medications
- Prior allogeneic Hematopoietic Stem Cell transplantation or solid organ transplantation
- Splenectomy
- Current splenomegaly or proliferative hematologic disease
- Inability or refusal to practice contraception during therapy; pregnancy
- History of medical or psychiatric disease which, in the view of principal investigator, would preclude safe treatment
- Cognitive impairment or likelihood of developing cognitive impairment during study
- Inability to give informed consent

4. STUDY DESIGN

- Phase I, inter-patient, dose escalation study assessing a two week treatment by CYT 99 007 given subcutaneously every other day
- Evaluation of Dose Limiting Toxicity (DLT) and Maximum Tolerated Dose (MTD)
- Five dose levels; patient assignment to dose level based on sequential order of entry; each dose level with a minimum of three patients enrolled.

- No entry to the next dose level until all previous dose level patients have reached day 28
- Continuation of therapy beyond day 28 is not allowable
- Patients will be evaluated at three and ix months after therapy for the identification of sub-acute or chronic toxicity and for immunogenicity

5. STUDY DRUG

CYT 99 007 is a non-glycosylated, human Interleukin-7 produced by recombined E.Coli. It is developed by trial sponsor Cytheris Inc. (Rockville, MD), under IND 10967, and manufactured under GMP conditions by Eurogentec S.A. (Searing, Belgium) under contract to Cytheris.

CYT 99 007 is supplied as a sterile white to off-white freeze-dried powder suitable for subcutaneous administration upon reconstitution and dilution. Drug is supplied in individually boxed single-use vials:

- 8 cc vials containing 1 mg of CYT 99 007 protein and 2 mg of sucrose
- 17 cc vials containing 4 mg of CYT 99 007 protein and 8 mg of sucrose

Drug administration

CYT 99 007 will be injected by subcutaneous route every other day for 2 consecutive weeks (15 days) for a total of 8 doses, at dose levels of 3, 10, 25, 50 and 100 µg/kg per dose.

6. RESPONSE CRITERIA

Definition of Toxicity (DLT & MTD):

- Using the NCI Common Toxicity Criteria

Definition of “Biologically Active Dose”

- A 50% increase in CD3 + T cells /mm³ determined by flow cytometry over the patient’s baseline CD3 + count
- Baseline will be defined in each patient as the mean number of CD3 + cells of four determinations over a period of no more than two weeks prior to “CYT 99 007” administration
- This study will aim at determining a *range* of biologically active doses

Secondary Clinical Study End-points

- Evaluation of response by RECIST criteria

Secondary Biologic Study End-points

- Increase in T cell cycling as evidenced by at least a three-fold increase in the number of CD4 or CD8 cells expressing Ki-67
- Enhancement of T cell function by potentiation of the response to OKT3 stimulation defined as:

- A four-fold decrease in the dose of stimulating antibody (OKT3) necessary to trigger 50% of the maximum proliferative response, or
 - A four-fold increase in absolute proliferation of enriched T cells in an OKT3 dose-response assay
- Determination of up-regulation in the Bcl-2 family of genes: 30% of cells have a significant increase in mean fluorescence intensity by FACS analysis of peripheral blood mononuclear cells